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Complications of Inappropriate Use of Spironolactone in Heart Failure: When an Old Medicine Spirals Out of New Guidelines

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OBJECTIVES This study was designed to investigate the appropriateness and complications of the use of spironolactone for heart failure (HF) in clinical practice.

BACKGROUND Spironolactone was reported by one prospective randomized trial to decrease morbidity and mortality in patients with New York Heart Association (NYHA) class III and IV HF. With this report (Randomized Spironolactone Evaluation Study [RALES] trial), we noted a marked increase in widespread use of spironolactone in patients with HF. Long-term outcome data with respect to safety and utilization of this medication in HF are not available.

METHODS To investigate the use of spironolactone for HF in a clinical setting, we analyzed the application of the RALES trial protocol to the care of 104 patients, whom we identified as being started on spironolactone for HF after prerelease of the RALES trial.

RESULTS We found broader use, less intensive follow-up, and increased complications with spironolactone treatment compared with the RALES trial. Cardiologists provided more appropriate care than did primary care providers.

CONCLUSIONS These data suggest that spironolactone is being used widely in HF without consideration of the NYHA class and ejection fraction, and without optimization of background treatment with angiotensin-converting enzyme inhibitors and beta-blockers. Clinical follow-up does not adhere to the RALES trial guidelines, resulting in higher complications. We conclude that long-term studies with further safety and efficacy data are needed. (J Am Coll Cardiol 2003;41:211–4) © 2003 by the American College of Cardiology Foundation

Spironolactone has been reported to reduce morbidity and mortality in patients with severe heart failure (HF) by a single, prospective, randomized large-scale trial, the Randomized Spironolactone Evaluation Study (RALES) (1). Patients enrolled in the RALES trial were strictly limited to those with advanced HF, normal serum potassium values, and normal or only mildly elevated serum creatinine levels. Moreover, in this study, spironolactone was used at very low doses, far less than the customary doses used for cirrhosis or hypertension (1).

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Spironolactone is a familiar diuretic for the primary care physician—easy to initiate, simple to titrate, and very reasonably priced (2). In contrast, though supported by a large body of literature, the initiation, titration, and monitoring of angiotensin-converting enzyme inhibitors and beta-blockers in HF can be difficult and time consuming (3,4). With the report of the RALES trial, we noted widespread use of spironolactone in patients with HF. Considering the difference in patients enrolled in trials and in clinical practice (5), we decided to investigate the appropriateness and complications of the use of spironolactone for HF in clinical practice.

METHODS

Study cohort and protocol. Of the 377 patients with new prescriptions for spironolactone after August 1, 1999, 110 were identified to be initiated for HF and constituted the study cohort. The date was chosen after the prerelease of the RALES trial on July 19, 1999, and subsequent media publicity (6). Retrospective medical record reviews were performed on all cohort patients. Inclusion criteria included patients initiated on spironolactone for HF between August 1, 1999, and January 1, 2000, and consent of the primary care providers for medical record review. Exclusion criteria included patients with chronic liver disease, portal hypertension, use of spironolactone for hypertension, or edema without HF. Patient records were reviewed for 12 months from the date of spironolactone initiation. Six patients were excluded because no follow-up data were available.

Study objectives. Primary objectives were to 1) Determine if patient selection adhered to the RALES criteria, which included: a) New York Heart Association (NYHA) class IV HF within six months; b) NYHA class III or IV HF at the time of enrollment; c) left ventricular ejection fraction (LVEF) <35% within six months; and d) exclusion of patients with a serum creatinine ≥2.5 mg/dl or a serum

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Abbreviations and Acronyms

ACC = American College of Cardiology
AHA = American Heart Association
BP = blood pressure
HF = heart failure
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RALES = Randomized Spironolactone Evaluation Study
SBP = systolic blood pressure

potassium >5 mmol/l. 2) Determine whether management followed the RALES trial criteria, which included: a) dosing of spironolactone at 25 to 50 mg/day; b) laboratory and clinic follow-up at four weeks and at three and six months; c) appropriate use of angiotensin-converting enzyme inhibitors and beta-blockers; d) discontinuation of potassium-sparing diuretics and potassium supplements, unless potassium was <3.5 mmol/l; e) holding spironolactone for hyperkalemia or creatinine >4 mg/dl. 3) Determine the incidence of the complications following spironolactone use, prospectively defined as development of the following: a) hyperkalemia with serum potassium ≥5.2 mEq/l or serious hyperkalemia ≥6.0 mEq/l; b) renal insufficiency with serum creatinine ≥2.0 mg/dl; and c) hyponatremia with serum sodium <135 mEq/l.

Secondary objectives were to determine 1) adverse events related to hyperkalemia, such as temporary pacemaker insertion for hemodynamically unstable bradyarrhythmia; 2) incidence of hypotension, defined as drop in systolic blood pressure (SBP) >15% compared with baseline and a SBP <90 mm Hg following spironolactone therapy; and 3) correlation between appropriate management index and specialization and training level of the providers.

This study was approved by the Baylor College of Medicine and VA Medical Center Institutional Review Board.

Statistical analysis. All data were expressed as mean ± SEM. The appropriate management index was calculated as the weighed cumulative effect of use of angiotensin-converting enzyme inhibitors, indicated NYHA or LVEF selection, and indicated lab and clinic follow-up for spironolactone use. Correlations were assessed by Spearman rank test (Sigmastat, SPSS).

Table 1. Patient Demographics

	Study Cohort (n = 104)	RALES trial (n = 822)
Age (yrs)	66.2 ± 10	66 ± 12
Male gender (%)	100	73
BP		
Systolic	127 ± 25	123 ± 21
Diastolic	72 ± 13	75 ± 12
LVEF (%)	27.2 ± 14.7	25.6 ± 6.7
Cause of HF (% ischemic)	55.8	55

Data ± SD.
BP = blood pressure; HF = heart failure; LVEF = left ventricular ejection fraction; RALES = Randomized Spironolactone Evaluation Study.

RESULTS

Patient demographics. Table 1 shows the baseline characteristics of patients in our cohort in comparison with the RALES trial. All of our patients were men, reflecting the Veterans Affairs Medical Center population. Baseline characteristics of age, LVEF, blood pressure (BP), and etiology of HF were similar to those in the RALES trial.

Patient selection and follow-up. As shown in Table 2, though almost all of the patients in the RALES trial were in NYHA class III-IV HF, 9% of our patients had documented NYHA class I to II at baseline and only 25.6% had the appropriate, documented NYHA class of III to IV. A total of 65.4% of our patients did not have any classification of NYHA before or after spironolactone initiation. Though the mean LVEF was similar to the RALES trial, only 54.8% of the cohort patients had documented LVEF of <35% before beginning spironolactone.

Overall, most patients were on optimal background therapy for HF: 80% were on angiotensin-converting enzyme inhibitors, 5% were on angiotensin receptor blockers, and 3% were on hydralazine and isosorbide combination. The mean daily doses of angiotensin-converting enzyme inhibitors were much higher than in the RALES trial, but closer to the target doses used in other studies and recom-

Table 2. Patient Selection and Follow-Up

	Study Cohort (n = 104)	RALES Trial (n = 822)
NYHA (% patients)		
I	4.5	0
II	4.5	0.5
III	15.3	72
IV	10.3	27
Undocumented	65.4	0
% Patients with LVEF < 35	54.8	100
Medications (% patients)		
Loop diuretics	90.4	100
ACE inhibitors	79.8	95
Digitalis	55.7	75
Potassium supplements	40.4	29
Beta-blockers	34.6	11
Mean dose of ACE inhibitors		
Captopril (mg/day)	120 ± 12	63.4
Lisinopril (mg/day)	23 ± 2	15.5
Mean dose of beta-blockers		
Metoprolol (mg/day)	72.3 ± 10	not reported
Mean dose of spironolactone (mg/day)	40.7 ± 3.1	26
% Patients continued on potassium supplements	40.4	29
% Patients with renal insufficiency at baseline	30.7	excluded
% Patients with diabetes mellitus	46.2	not reported

ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; other abbreviations as in Table 1.

mended by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (7). The mean daily dose of spironolactone in our cohort (40.7 ± 3.1 mg) was also much higher than the dose used in the RALES trial (26 mg). Thirty-five percent of our patients were on beta-blockers and 40% of the patients were continued on potassium supplements despite absence of hypokalemia. At baseline, 31% of our patients had renal insufficiency and 46% had diabetes mellitus. Only 38% of our patients had appropriate laboratory and 34% appropriate clinical follow-up.

Adverse events. Twenty-four percent (n = 25) of our patients developed hyperkalemia (levels ≥5.2, normal potassium values at our laboratory: 3.5–5.1 mEq/l). Twelve percent (n = 12) developed serious hyperkalemia (levels ≥6 mEq/l), compared with only 2% reported in the RALES trial. Thirty-one percent (n = 32) developed hyponatremia, and 25% (n = 26) developed renal insufficiency. Only 2% of our patients, compared with 10% in the RALES study, developed gynecomastia. Seven percent (n = 7/104) of our patients developed hypotension and 3% (n = 3/104) required temporary pacemaker insertion for hemodynamically unstable bradyarrhythmia related to serious hyperkalemia such as complete heart block, Mobitz type II atrioventricular block, or pauses ≥3 s. Twenty-one percent of our patients were subsequently discontinued from spironolactone compared with 8% in the RALES trial.

Provider type. Providers were ranked into five categories according to their specialty, affiliation and training: academic staff cardiologist, noncardiology academic staff, medical residents, noncardiology medical staff at community clinics, and physician's assistants.

As shown in Figure 1, the staff cardiologists, followed by the academically affiliated noncardiology staff members and medical residents, had better profiles in appropriate management of spironolactone treatment in patients with HF than did other primary care providers. There was a significant correlation between provider type rank and appropriate management index, with a correlation coefficient of 0.2 and p value of 0.04.

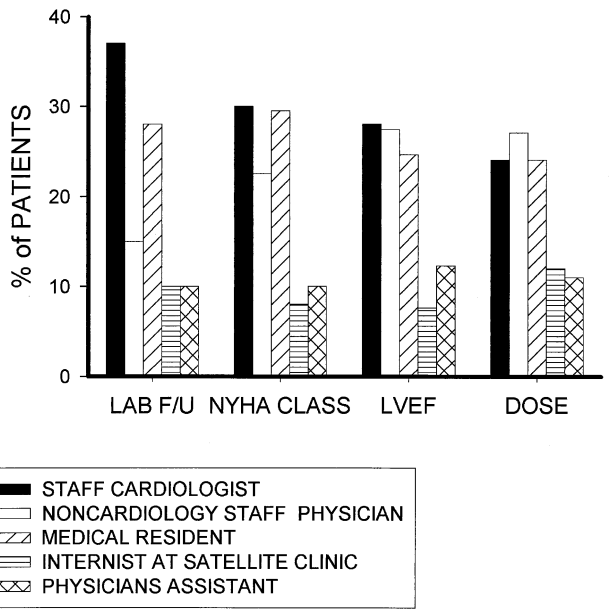

Figure 1. Differences in appropriate patient selection and management with spironolactone according to provider type. The providers are ranked as the staff cardiologist, noncardiology academic staff member, medical resident, satellite clinic nonacademic internist, and the physician assistant. Vertical axis represents the % of patients in our cohort adhering to RALES trial management guidelines for appropriate laboratory follow-up (LAB F/U) (at four weeks and three and six months), New York Heart Association (NYHA) class selection (class III to IV), left ventricular ejection fraction (LVEF) selection (<35%), and the mean daily dose (25 to 50 mg/day) for spironolactone use in patients with heart failure.

DISCUSSION

Our study reveals that complications with spironolactone use in patients with HF are greater in clinical practice than reported in a rigorous trial. According to our results, part of the reason is broad use of this medication and lack of appropriate follow-up of the patients. The relative familiarity of primary care providers with spironolactone for other indications, as well as the low cost and ease of titration of this medication, probably make it readily applicable for HF. However, providers appear to have difficulty adhering to new indication guidelines and resort to their customary prescription and management habits.

There were a number of striking differences between the patterns of use of spironolactone for HF in our hospital and the RALES trial. Although patients were similar in age, baseline BP, and etiology of HF, only a small percent of our patients were in NYHA class III to IV and had documented low LVEF. The average daily dose of spironolactone prescribed in our cohort far exceeded the dose in the RALES trial, and more patients in our cohort were continued on potassium supplements despite the absence of hypokalemia. Likewise, the clinical and laboratory follow-ups were not as rigorous as in the RALES trial.

Adverse outcome rates, especially hyperkalemia, exceeded those reported in the RALES trial for several reasons. First, the higher angiotensin-converting enzyme inhibitor doses used in our study, closer to the recommended target doses, may have resulted in more hyperkalemic complications. Second, more patients with baseline renal insufficiency were started on spironolactone, and potassium supplements or potassium-sparing diuretics were not adjusted. Third, half of our patients had diabetes and may be prone to hyporeninemic hypoaldosteronism and hyperkalemia. These findings, however, are similar to other studies reporting life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone (8–10). Thus, the long-term safety of combination therapy in HF with high-dose angiotensin-converting enzyme inhibitors, digoxin, beta-blockers, and spironolactone is not well established and needs careful monitoring.

According to our study, cardiologists provided more appropriate care in selection and follow up of patients with HF on spironolactone. As suggested by this and other studies (11–13), the sophisticated treatment regimen with increasing number of medications in HF may require input or close monitoring of a specialist or multidisciplinary team. With the results of this study, there was an overall change in patient management at our hospital. A quality improvement team was formed providing education and feedback on spironolactone use in HF, and these patients on discharge were referred to a HF specialty clinic with a cardiologist.

One of the great challenges of medical research is to translate findings into clinical practice. Though beta-blockers have been demonstrated to be beneficial in HF by numerous large-scale clinical trials (4), and are recommended as standard therapy (7), only 34.6% of our patients placed on spironolactone were on beta-blockers. ACC/AHA HF guidelines recommend spironolactone to be initiated only in selected patients after optimal background therapy including angiotensin-converting enzyme inhibitors and beta-blockers (7). Our data demonstrate that physicians initiate spironolactone before beta-blockers in a significant number of patients. This likely reflects the greater difficulty in starting beta-blocker therapy, and the need for frequent follow-up visits to cautiously titrate the dose. As suggested by Ghali et al. (6), our results also raise the concern that high levels of publicity created by media coverage, quoting only the summary of findings of a study, may have resulted in early but oversimplified adoption of a sophisticated treatment strategy.

We conclude that long-term studies are needed, with further data on safety and efficacy of optimal combination therapy with spironolactone in HF. High-risk patients on multiple medications not commonly represented in randomized trials may need to be followed up more closely with regard to safety and medication interaction.

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